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van Dijk, Marlies; Hartman, Jorine E; Klooster, Karin; Ten Hacken, Nick H T; Kerstjens, Huib A M; Slebos, Dirk-Jan

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Endobronchial Valve Treatment in Emphysema Patients with a Very Low DLCO

Marlies van Dijk Jorine E. Hartman Karin Klooster Nick H.T. Ten Hacken
Huib A.M. Kerstjens Dirk-Jan Slebos

University of Groningen, Department of Pulmonary Diseases, University Medical Center Groningen, Groningen Research Institute for Asthma and COPD, Groningen, The Netherlands

Keywords
Chronic obstructive pulmonary disease · Endobronchial valve treatment · Bronchoscopic lung volume reduction · Diffusing capacity

Abstract
Background: For selected patients with severe emphysema, bronchoscopic lung volume reduction with endobronchial valves (EBV) is recognized as an additional treatment option. In most trials investigating EBV treatment, patients with a very low diffusing capacity (DLCO) were excluded from participation. ***Objectives:*** Our goal was to investigate whether EBV treatment in patients with emphysema with a very low DLCO is safe and effective. ***Methods:*** This was a single-center retrospective analysis including patients with emphysema and a DLCO ≤20%pred who underwent EBV treatment. Follow-up was performed 6 months post-treatment. Outcome parameters were compared to a historical matched control group (DLCO >20%pred, matched for sex, age, forced expiratory volume in 1 s [FEV_1], and residual volume [RV]). ***Results:*** Twenty patients (80% female, 64 ± 6 years, FEV_1 26 ± 6%pred, RV 233 ± 45%pred, DLCO 18 ± 1.6%pred) underwent EBV treatment. At 6 months follow-up, we found a statistically significant improvement in FEV_1 (0.08 ± 0.12 L), RV (–0.45 ± 0.95 L), 6-min walking distance (38 ± 65 m), and St. George's Respiratory Questionnaire (–12 ± 13 points). With the exception of FEV_1, all exceeded the minimal clinically important difference. The most common serious adverse event was a pneumothorax requiring intervention (15%). There were no significant differences in outcome compared to the DLCO >20%pred control group. ***Conclusions:*** In this single-center retrospective analysis, we showed statistically significant and clinically relevant improvements in lung function, exercise capacity, and quality of life up to 6 months after EBV treatment in emphysema patients with a DLCO ≤20% (14–20%) of predicted with no increased risk of serious adverse events.

Introduction

In advanced chronic obstructive pulmonary disease (COPD), breathlessness, impaired exercise capacity, and poor quality of life are common despite optimal standard therapy [1]. For selected patients with advanced COPD, bronchoscopic lung volume reduction with endobron-

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E-Mail karger@karger.com
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Marlies van Dijk, MD
Department of Pulmonary Diseases, AA11
University Medical Center Groningen
PO Box 30001, NL–9700 RB Groningen (The Netherlands)
E-Mail m.van.dijk05@umcg.nl

chial valves (EBV) is recognized as an additional treatment option [2]. Prerequisites for this treatment are the presence of emphysema, severe hyperinflation, and absence of collateral ventilation between the target lobe and ipsilateral lobe(s) [3]. EBV treatment has emerged in recent years as a less invasive alternative for lung volume reduction surgery and has been shown to improve lung function, exercise capacity, and quality of life [4–8].

In most research investigating EBV treatment, patients with a very low diffusing capacity of the lungs for carbon monoxide (DLCO) were excluded from participating. This is mostly due to the results of the National Emphysema Treatment Trial (NETT), a large international multicenter trial comparing lung volume reduction to standard of care, where a subgroup of high-risk patients was identified with an increased postoperative mortality rate [9, 10]. These high-risk patients were defined by having a forced expiratory volume in 1 s (FEV_1) of 20% or less of the predicted value combined with either a homogeneous distribution of emphysema or a DLCO of ≤20% of predicted (%pred). However, a recent retrospective trial investigating lung volume reduction surgery in patients with a DLCO of <20%pred showed positive effects of treatment with no increased mortality rate (90-day mortality 0%) [11].

To our knowledge, no study evaluating outcomes in patients with a very low DLCO undergoing EBV-treatment has been published so far. Our goal was to investigate whether patients with COPD and a very low DLCO have the same clinical benefits as patients with a DLCO above 20%pred and whether these patients are at increased risk of serious adverse events (SAEs). Furthermore, in the group of patients with a very low DLCO, we performed subanalyses for multiple patient characteristics relating to reduced oxygen uptake and emphysema distribution to assess whether these were associated with differences in outcome of EBV treatment.

Material and Methods

Study Design and Population

This was a single-center retrospective analysis including patients with COPD and a DLCO ≤20%pred who underwent bronchoscopic lung volume reduction with EBV at our hospital between April 2016 and October 2018. All patients with a DLCO ≤20%pred who were treated in our hospital and registered in the BREATH-NL Registry (NCT02815683) or participated in a clinical trial (NCT02022683) were included. A historical control group of patients treated in our hospital with a DLCO ≥20%pred was selected from the BREATH-NL Registry. These control patients were matched for sex, age, FEV_1, and residual volume (RV). During the selection process, all outcome parameters were blinded. All subjects signed informed consent.

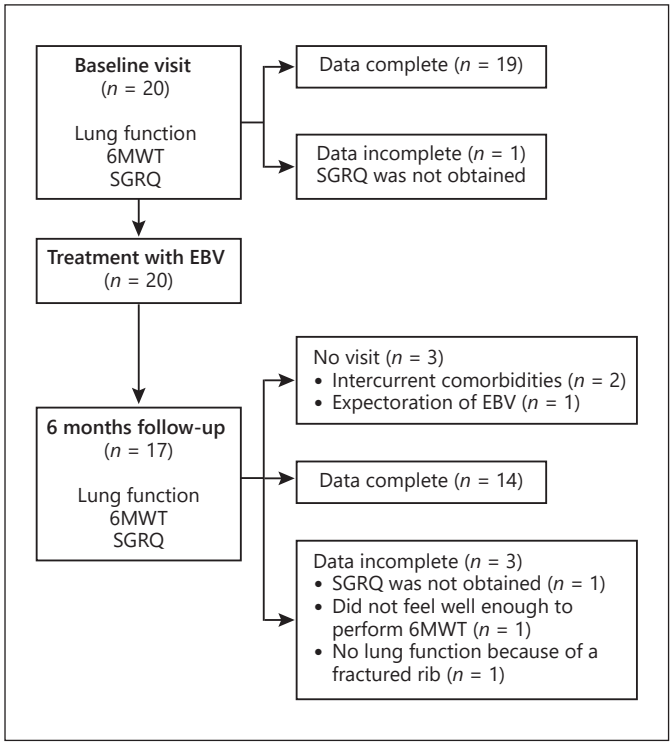

Fig. 1. Study flowchart for patients with a DLCO ≤20%pred. EBV, endobronchial valve; SGRQ, St. George's Respiratory Questionnaire; 6MWT, 6-min walking test.

Measurements

Post-bronchodilator spirometry, body plethysmography, and diffusion capacity were measured using the Jaeger MasterScreen™ (CareFusion, Germany) and were performed according to the ATS/ERS guidelines using the reference values from the European Community for Coal and Steel [12–14]. Spirometry and body plethysmography were performed at baseline and 6 months after treatment. The 6-min walking test was performed at baseline and 6 months and done in accordance with ATS recommendations [15]. The St. George's Respiratory Questionnaire (SGRQ) was used to measure health-related quality of life [16] and was obtained at baseline and 6 months follow-up. Arterial blood gas analysis, high-resolution CT scan, quantitative CT analysis, and echocardiogram were performed at baseline.

Treatment

All bronchoscopic procedures were performed according to current best practice recommendations and all under general anesthesia [17]. A Chartis measurement (Chartis®, Pulmonx Corporation, Redwood City, CA, USA) was performed to assess collateral ventilation between the target lobe and ipsilateral lobe(s). In the absence of collateral ventilation, EBV (Zephyr® EBV, Pulmonx Corporation, Redwood City, CA, USA) were placed in all segments or subsegments of the target lobe.

Table 1. Baseline characteristics

Baseline characteristic	Patients with a DLCO ≤20%pred (n = 20)	Patients with a DLCO >20%pred (historical matched control group, n = 20)
Female, n (%)	16 (80)	16 (80)
Age, years	64±6	62±7
Body mass index	21±2.7	23±3.1
Cigarette smoking, pack-years	44±19	51±27
FEV_1		
Liters	0.58±0.14	0.61±0.13
Percentage of predicted	23±4	24±4
FVC		
Liters	2.15±0.74	2.30±0.48
Percentage of predicted	70±17	76±15
RV		
Liters	5.26±0.92	5.24±1.30
Percentage of predicted	252±46	252±49
TLC		
Liters	7.77±1.28	7.77±1.50
Percentage of predicted	141±13	142±18
Ratio of RV to TLC, %	68±7	67±5
Carbon monoxide diffusing capacity,	1.49±0.27	2.31±0.65
mmoL/(min×kPa)	18±1.6 (range 14–20)	29±6
Percentage of predicted value		
Arterial blood gas, kPa		
PaO_2	8.4±1.2	8.9±1.5
$PaCO_2$	5.6±0.7	5.6±0.68
$p(A\text{-}a)O_2$ gradient	4.5±1.1	4.1±1.5
6-min walking test		
Distance, m	287±91	320±82
Pre-test oxygen saturation, %	95±2	95±2
Post-test oxygen saturation, %	86±7	89±5
Questionnaires		
SGRQ, points	58±14	57±13
mMRC, points		
2	7 (35%)	5 (25%)
3	9 (45%)	14 (70%)
4	4 (20%)	1 (5%)
HRCT findings		
Target lobe		
RUL	4	6
RUL+RML	0	0
RML	1	1
RLL	3	5
LUL	5	4
LLL	7	4
Target lobe volume, mL	1,698±439	1,642±458
Target lobe voxels below –950 HU, %	46±6	44±6
Emphysema distribution, n (%)		
Homogeneous	13 (65)	12 (60)
Heterogeneous	7 (35)	8 (40)

Data represented as mean ± SD unless otherwise specified. Heterogeneous emphysema was defined as a difference between the target lobe and ipsilateral lobe(s) ≥15% in voxels below –950 HU on HRCT. There were no statistically significant differences in baseline characteristics, with the exception of DLCO as per study design. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; SGRQ, St. George's Respiratory Questionnaire; mMRC, modified Medical Research Counsel; HRCT, high-resolution computed tomography; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe.

Responders

A patient was considered a responder to treatment if the FEV_1, RV, 6-min walking distance (6MWD), or SGRQ improved more than the minimal clinically important difference (MCID) after treatment. The following MCIDs were used: relative change in FEV_1 ≥12%, a decrease in RV of ≥430 mL, an increase in 6MWD of ≥26 m, and a decrease of SGRQ total score of 4 or 7 points [18–22].

Table 2. Change in clinical outcomes 6 months after EBV treatment

Variable	Patients with DLCO ≤20%, 6 months FU (n = 17)	Patients with DLCO >20%, 6 months FU (n = 19)	DLCO ≤20 vs. >20%, p value
ΔFEV_1, L (relative increase, %)	+0.08±0.12 (14±23)*	+0.18±0.16 (28±20)	0.09
ΔFVC, L (relative increase, %)	+0.28±0.41 (15±22)*	+0.48±0.60 (22±25)	0.40
ΔRV, L (relative increase, %)	−0.45±0.95 (−9±18)*	−0.74±0.78 (−13±14)	0.50
ΔTLC, L (relative increase, %)	−0.25±0.69 (−3±9)*	−0.38±0.52 (−5±6)	0.82
ΔRV/TLC, %	−5±7*	−6±7	0.53
Δ6MWD, m	+37±67*	+40±83	0.93
ΔSGRQ, points	−12±14*	−10±16	0.71

Change in lung function, 6MWD and SGRQ total score after EBV treatment for patients with a DLCO ≤20% of predicted and patients with a DLCO >20% of predicted. Data represented as mean ± SD. FU, follow-up; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; 6MWD, 6-min walking distance; SGRQ, St. George's Respiratory Questionnaire. * Significant improvement within the DLCO ≤20% group over 6 months ($p < 0.05$). There were no significant differences between change in outcomes 6 months after treatments between patients with a DLCO ≤20% and the control group (DLCO >20%).

Subanalyses

Subanalyses were performed to assess whether there was a difference in outcome when patients (with a DLCO ≤20%pred) were divided into groups based on baseline partial pressure of oxygen in arterial blood on room air (PaO_2; ≥8.0 kPa [60 mm Hg] or <8.0 kPa), oxygen saturation (StO_2) post 6MWD (≥88 or <88%), distribution of emphysema (heterogeneous when difference between target and ipsilateral lobe voxels below −950 Hounsfield units on high-resolution CT scan ≥15 percentage point, otherwise homogeneous), or presence of pulmonary hypertension (right ventricular peak pressure <25 or ≥25 mm Hg on echocardiogram).

Statistics

A Wilcoxon signed ranks test was performed to evaluate the difference in lung function, exercise capacity, and quality of life between baseline and 6 months follow-up. A Mann-Whitney U test was performed for the comparison of outcome parameters between patients with a DLCO ≤20% vs. DLCO >20% and also for the subgroup analyses. When follow-up data (FEV_1, RV, 6MWD, or SGRQ) were missing, the patient was considered to be a nonresponder. A p value of <0.05 was considered statistically significant. IBM SPSS Statistics version 23 (IBM, Armonk, NY, USA) was used for all analyses.

Results

Twenty patients with advanced COPD and a DLCO ≤20%pred underwent EBV treatment at our hospital (80% female, 58 ± 8 years, FEV_1 26 ± 6%pred, RV 233 ± 45%pred). See study flowchart in Figure 1, and baseline characteristics in Table 1. Except for DLCO ($p < 0.001$), there were no significant differences between baseline characteristics for the patient group with a DLCO ≤20%pred and the control group with a DLCO >20%pred (Table 1).

At 6 months follow-up, there was a statistically significant improvement in all lung function parameters, 6MWD, and the SGRQ total score compared to baseline measurements (Table 2). RV (−0.45 ± 0.95 L), 6MWD (38 ± 65 m), and SGRQ score (−12 ± 13 points) improved more than the MCID. This was not the case for FEV_1 (0.08 ± 0.12 L). Responder rates at 6 months for the patient group with a DLCO ≤20%pred for FEV_1, RV, SGRQ (−4 points), SGRQ (−7 points), and 6MWD were 45, 40, 65, 50, and 45%, respectively (Fig. 2). There were no statistically significant differences in lung function parameters, 6MWD, SGRQ total score, and responder rate between the patient group with a DLCO ≤20%pred and the control group with a DLCO >20%pred (Table 2).

No patients died in both the group of patients with a DLCO ≤20%pred and the control group during 6 month follow-up. In the group of patients with a DLCO ≤20%pred, a pneumothorax, for which a chest tube insertion was needed, did occur in 3 cases (15%), all within 4 days after the procedure. In one of these cases, temporary removal of EBV and video-assisted thoracic surgery was additionally performed to resolve the pneumothorax. Three other patients had a small pneumothorax not requiring intervention. Three patients developed a COPD exacerbation requiring hospital admission (15%). Three patients (15%) required additional bronchoscopies for valve replacement. One patient (5%) required removal of all valves be-

Table 3. Serious adverse events after EBV treatment

Serious adverse event	SAEs in patients with a DLCO ≤20% (n = 20), n (%)	SAEs in patients with a DLCO >20%pred (n = 20), n (%)	Reported SAEs [4–8] in the literature, min–max %
Pneumothorax			
Requiring chest tube drainage	3 (15)	2 (10)	14.7–29.6
Hospital admission for COPD exacerbation	3 (15)	1 (5)	9.8–34.9
Revision bronchoscopy			
For replacement or temporal removal of valve(s)	3 (15)	5 (25)	6–20
For permanent removal of valves	1 (5)	1 (5)	1.5–20.5
Pneumonia	0 (0)	2 (10)	0–10
Death	0 (0)	0 (0)	1.5–10

Serious adverse events (SAEs) during 6 months follow-up for patients with a DLCO ≤20% (n = 20) and patients with a DLCO >20%pred (n = 20) and reported SAEs in RCTs investigating bronchoscopic lung volume reduction with endobronchial valves with a 3–12-month follow-up. There were no statistically significant differences between SAEs for patients with a DLCO ≤20% and patients with a DLCO >20%pred.

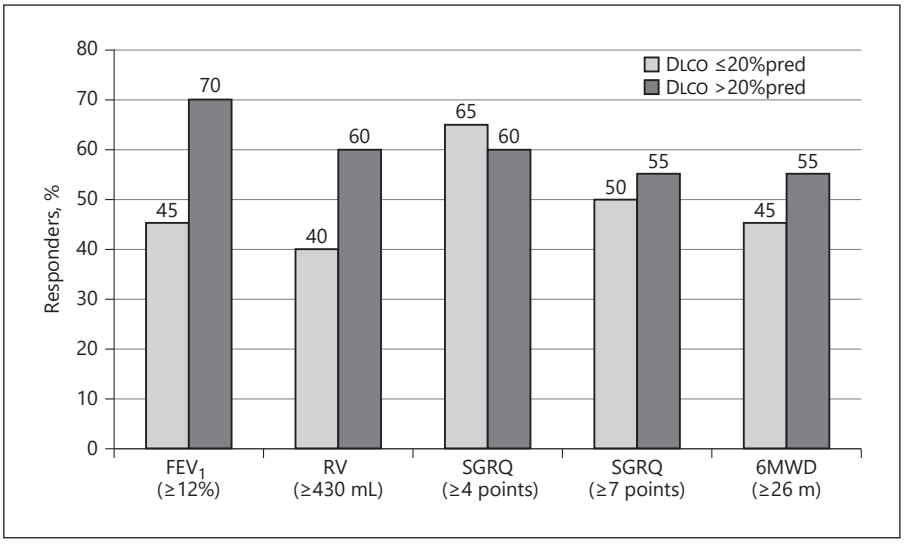

Fig. 2. Responder rates at 6 months follow-up for patients with a DLCO ≤20%pred (n = 20) and DLCO >20%pred (n = 20). Responders were defined as having an improvement equal to or greater than the minimal clinically important difference for FEV_1 (≥12%) [18], RV (≥430 mL) [19], SGRQ (≥4 points) [21], SGRQ (≥7 points) [22], or 6MWD (≥26 m) [20]. There were no significant differences in responder rates for patients with a DLCO ≤20%pred and DLCO >20%pred. FEV_1, forced expiratory volume in 1 s; RV, residual volume; 6MWD, 6-min walking distance; SGRQ, St. George's Respiratory Questionnaire.

cause of valve migration and consequently loss of atelectasis due to extensive granulation tissue. No pneumonias were reported. No statistically significant differences were found for SAEs between the patients with a DLCO ≤20%pred and the control group (Table 3).

Subgroup analyses for patients with a DLCO ≤20%pred divided into groups based on emphysema distribution (homogeneous n = 11; heterogeneous n = 5), baseline PaO_2 (≥8.0 kPa n = 11; <8.0 kPa n = 5), baseline StO_2 after 6-min walking test (≥88% n = 9; <88% n = 7) and presence of pulmonary hypertension on baseline echocardiography (RV peak pressure <25 mm Hg n = 6; RV peak pressure ≥25 mm Hg n = 10) revealed no statistically significant differences for change in lung function parameters, SGRQ scores, and 6MWD at 6 months follow-up, with the exception of improvement of forced vital capacity (FVC) in participants without pulmonary hypertension versus participants with pulmonary hypertension (ΔFVC +0.53 ± 0.29 L vs. +0.14 ± 0.42 L, p = 0.045).

Discussion/Conclusion

To our knowledge, this is the first study investigating EBV treatment in COPD patients with a very low DLCO, that is, 20%pred or lower. We found a statistically signif-

icant improvement of lung function, 6MWD, and quality of life 6 months after EBV treatment. Improvement of RV, 6MWD, and SGRQ score were greater than the established MCID. Furthermore, there were no statistically significant differences in change in lung function, 6MWD, SGRQ, and responder rates and SAEs between the low DLCO group and the matched control group with a DLCO >20%pred. The most common SAE was a pneumothorax requiring chest drainage (15%). Subanalyses of patients with a DLCO ≤20%pred divided into groups based on baseline characteristics that associate with reduced oxygen uptake and emphysema distribution showed no relevant differences on these outcomes.

There was a trend towards a larger increase in FEV_1 in patients with a DLCO >20 vs. ≤20%pred (+0.18 ± 0.16 vs. +0.08 ± 0.12, $p = 0.08$) and a higher responder rate for FEV_1 in the DLCO >20%pred group (FEV_1 70 vs. 45%, $p = 0.11$), but notably this was not reflected in a greater improvement in exercise capacity (6MWD) or quality of life (SGRQ).

A recently published pooled analysis of 6 randomized controlled trials investigating EBV treatment (in patients with a DLCO ≥20%pred) showed an improvement in FEV_1 (+21.8% relative increase), RV (–0.58 L), 6MWD (+49 m), and SGRQ score (–9.1 points) 3–12 months after EBV treatment [23]. These results are somewhat better than our 6-month follow-up results for patients with a DLCO ≤20%pred (FEV_1 +16% relative increase, RV –0.45 L, 6MWD +38 m, SGRQ –12 points). This may be explained by the fact that only patients with heterogeneous emphysema were included in 4 of the 6 trials, whereas in our study, 65% of patients with a DLCO ≤20%pred had a homogeneous distribution of emphysema.

The responder rates for FEV_1, RV, SGRQ (–4 points), and 6MWD for patients with a DLCO ≤20%pred at 6 months follow-up were 45, 40, 65, and 45%, respectively. The responder rates are within the range of responder rates published in recent RCTs (FEV_1 37–72%, SGRQ 56–79%, and 6MWD 42–87%) [4, 6–8], with the exception of responder rate for RV, which is slightly lower (44–71%). It is important to note that our responder rates may be a conservative estimate, since all participants with missing data were considered to be nonresponders. Furthermore, for patients with severe COPD, an MCID of 7 points on SGRQ total score has been shown to be more applicable to this patient group and treatment [22]. The incidence rate of SAEs in the patients group with a DLCO ≤20%pred was comparable to recent literature investigating EBV treatment (Table 3) [4–8].

In studies investigating EBV treatment, patients with a very low DLCO were often excluded. This may not be surprising since DLCO has been associated with an increased likelihood of hypoxemia and is a known unfavorable prognostic factor in COPD [24, 25]. Furthermore, as mentioned in the introduction, the multicenter NETT trial investigating lung volume reduction surgery identified a group of high-risk patients with an FEV_1 <20%pred and either a homogeneous distributed emphysema or a DLCO ≤20% who had increased 30-day mortality rates (16%) [9]. However, patients fulfilling the NETT high risk criteria have more recently been demonstrated to be able to have good effects from lung volume reduction surgery with no increased mortality rate [11, 26]. Furthermore, EBV treatment in patients with a FEV_1 ≤20%pred has been shown to be safe and effective [27, 28], and our study shows good results for EBV treatment in patients with a DLCO ≤20%pred.

The measurement of DLCO is used as an indication for functional gas exchange surface in the lung [29]. In emphysema, there is loss of gas exchange surface, and an inverse linear relation between DLCO and severity of emphysema on CT has been established [30]. However, in COPD, other factors such as ventilation/perfusion (V/Q) disturbances, inhomogeneous ventilation, and airway obstruction can influence the outcome of the DLCO measurement both negatively and positively [31–33]. The measured DLCO for a patient with COPD is therefore likely to be a balance of these factors. COPD is a heterogeneous disease, so while in one patient, the outcome of DLCO may be mainly due to loss of gas exchange surface, in the next patient, airway obstruction and V/Q disturbances may be the driving factors influencing DLCO.

We propose that the chance of successful EBV treatment in patients with a very low DLCO is related to the balance of factors causing the DLCO to be low. Factors we consider favorable in clinical practice are a high destruction level of the target lobe on chest CT and an FEV_1 larger than 20% of the predicted value. Factors we consider unfavorable are a homogeneous distribution of emphysema, significant target lobe perfusion, an important hypoxemia (i.e., PaO_2 <8.0 kPa or 60 mm Hg), significant desaturation during exercise, and pulmonary hypertension. We take every factor into account, and no single factor is an absolute contraindication. It is important to note that there is no scientific literature to support the use of these factors for clinical decision-making.

Our study did have some limitations. First of all, this is a retrospective analysis. However, we did include a well-matched control group with a significantly higher

DLCO to compare outcome parameters to. Furthermore, to prevent selection bias as much as possible, all patients with a DLCO ≤20%pred who underwent EBV treatment in our hospital were included. Nevertheless, there were emphysema patients with a very low DLCO, who were assessed but not accepted for EBV treatment. Another limitation is that our group of patients is relatively small. For the subgroup analyses that were performed, the number of patients was likely too small to exclude relevant statistically significant differences. Also, the factors for which subanalyses were performed are also factors we take into account in our clinical decision-making whether or not to treat an individual patient. However, since only a minority of patients with COPD who undergo EBV treatment have a DLCO ≤20%pred, it may be challenging to investigate a larger group of patients. Furthermore, there is a risk of bias because of missing data. Therefore, as mentioned above, with regard to responder rates, we considered participants to be nonresponders if data was missing. Finally, since no measurement of DLCO or arterial blood gas analysis was performed during follow-up, no information is available on change in DLCO or gas exchange after EBV treatment.

In conclusion, we found statistically significant and clinically relevant improvements in lung function, exercise capacity, and quality of life up to 6 months after EBV treatment in COPD patients with a DLCO ≤20%pred, with no increased risk of SAEs in this single-center retrospective analysis. No factors influencing the chance of a successful treatment could be identified in this group of participants. However, since the investigated subgroups were small, it is too soon to draw any definitive conclusions on the latter subject. It would be interesting to investigate whether long-term follow-up of EBV treatment is comparable for COPD patients with and without a very low DLCO. Furthermore, future research investigating factors influencing the likeliness of successful EBV treatment in COPD patients with a very low DLCO could greatly help clinicians in deciding whether or not EBV treatment is suitable for their patient.

Statement of Ethics

All patients signed informed consent and this study was approved by the Ethics Committee (NCT02815683 and NCT02022683).

Disclosure Statement

M.v.D., J.E.H., K.K., N.H.T.T.H., and H.A.M.K. have no conflict of interest. D.-J.S. is an investigator, physician advisor, and consultant for PulmonX Inc. CA, USA. No funding was received for this study.

Author Contributions

M.v.D. contributed to the trial design, analysis of data, preparation of the "Results" section and tables, and the writing of the manuscript and is the guarantor of the manuscript. J.E.H. contributed to the analysis of the data and the discussion and revisions of the manuscript. K.K. contributed to the discussion and revisions of the manuscript. N.H.T.T.H. contributed to the discussion and revisions of the manuscript. H.A.M.K. contributed to the discussion and revisions of the manuscript. D.-J.S. contributed to the trial design and the discussion and revisions of the manuscript.

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